Medicinal Chemistry

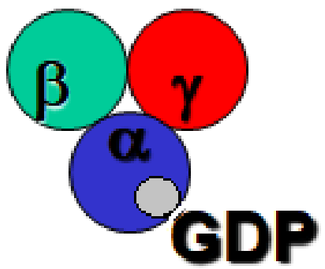
Chapter 6

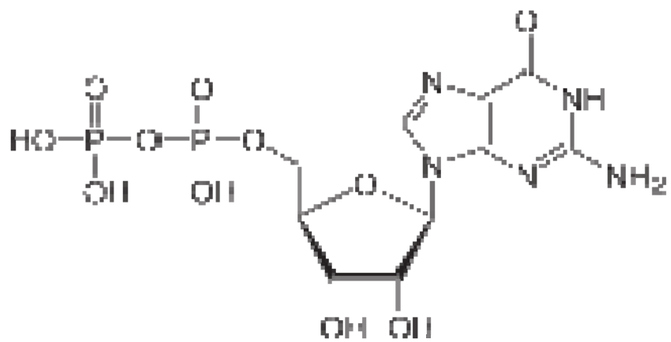
DRUG TARGETS: SIGNAL TRANSDUCTION

Contents

1. Signal Transduction involving G_s-Proteins

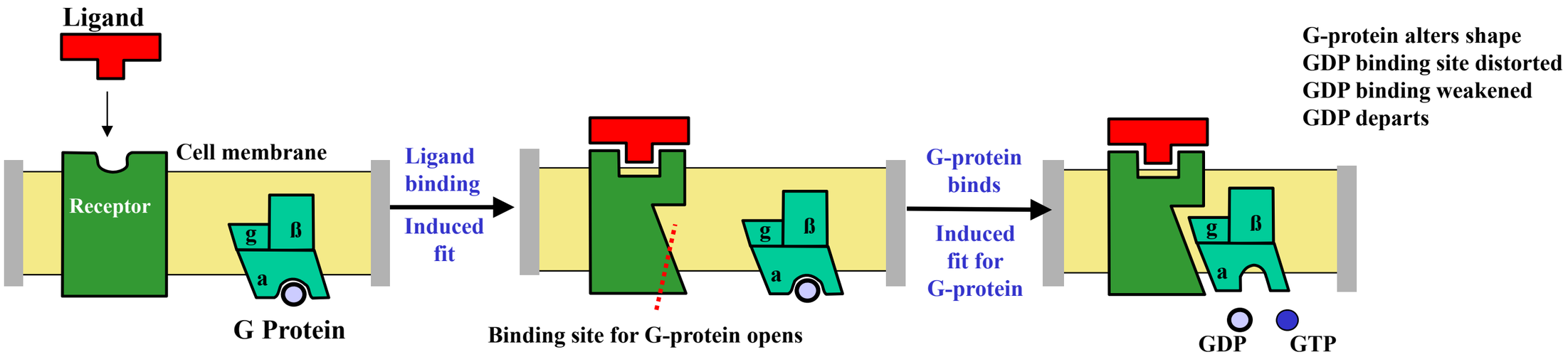
- G-proteins are membrane-bound proteins situated at the inner surface of the cell membrane
- and are made up of three protein subunits (α, β, and γ)
- The α-subunit has a binding pocket which can bind **guanyl nucleotides** and which binds **guanosine diphosphate** (GDP) when the G-protein is in the resting state.
- the G-protein acts as a molecular 'relay runner' carrying the message received by the receptor to the next target in the signal- ling pathway.



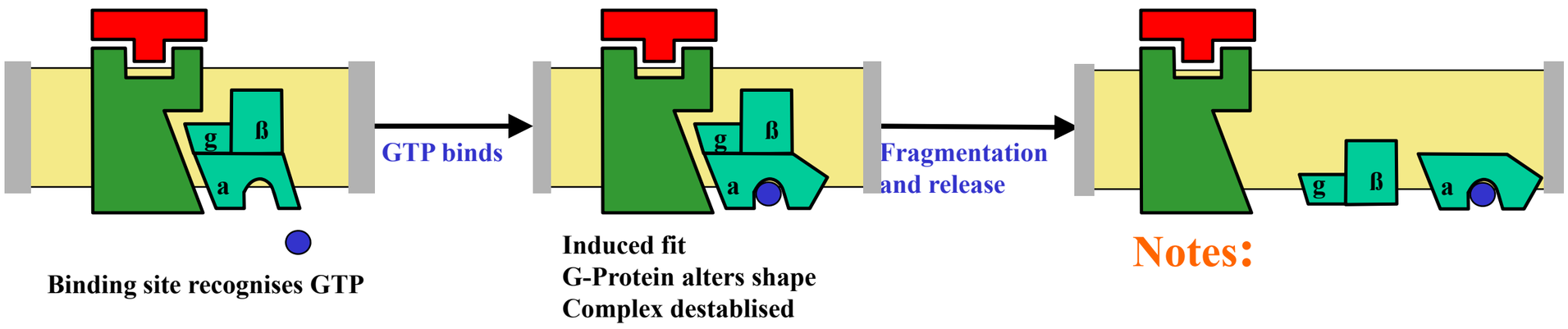


1.1 Interaction of receptor with G_s-protein

1. The receptor binds its neurotransmitter or hormone
2. The receptor changes shape and exposes a new binding site on its inner surface
3. The newly exposed binding site now recognizes and binds a specific G-protein and causes change in shape which, in turn, **changes the shape of the guanyl nucleotide binding site.**
4. This weakens the intermolecular bonding forces holding GDP and so GDP is released

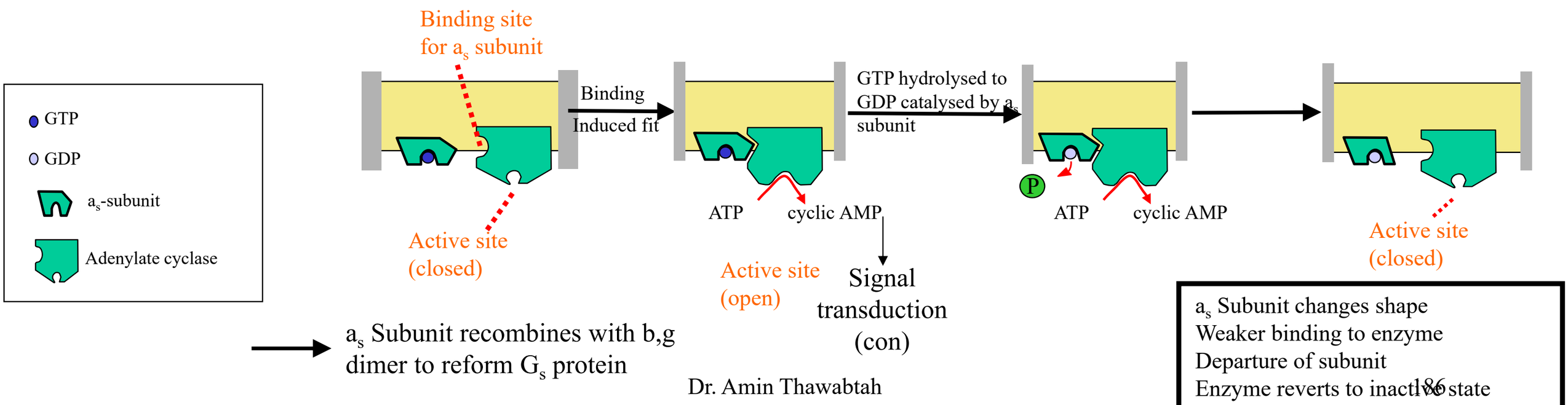


5. The binding pocket does not stay empty for long because it is now the right shape to bind GTP (guanosine triphosphate). Therefore, GTP replaces GDP causes another conformational change in the G-protein which weakens the links between the protein subunits such that the α-subunit (with its GTP attached) splits off from the β and γ-subunits
6. Both the α-subunit and the βγ-dimer then depart the receptor.
7. as Subunit carries message to next stage



1.2 Interaction of α_s with adenylate cyclase

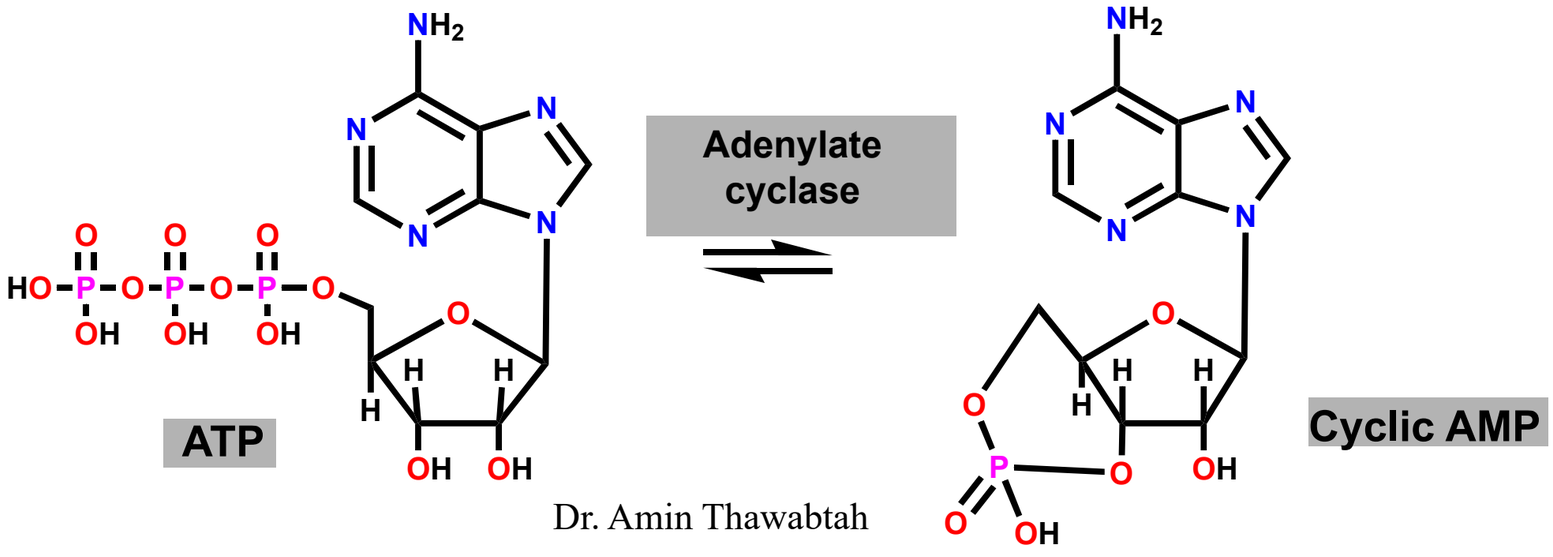
1. The α_s-subunit binds to a membrane-bound enzyme called adenylate cyclase (or adenylyl cyclase) and 'switches' it on
2. This enzyme now catalyses the synthesis of a molecule called cyclic AMP (cAMP)
3. The α_s-subunit has intrinsic GTP-ase activity (it can catalyse the hydrolysis of its bound GTP to GDP) and so it deactivates itself after a certain time period and returns to the resting state.
4. The α_s-subunit then departs the enzyme and recombines with the $\beta\gamma$-dimer to reform the Gs-protein while the enzyme returns to its inactive conformation.



1.2 Interaction of α_s with adenylate cyclase

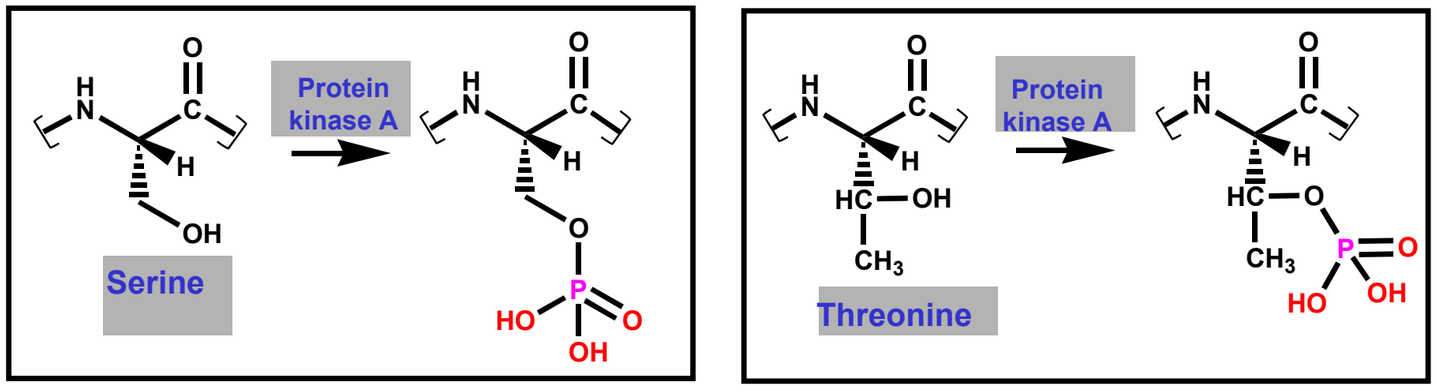
Notes:

- **Several 100 ATP molecules converted before α_s-GTP deactivated**
- **Represents another signal amplification**
- **Cyclic AMP becomes next messenger (secondary messenger)**
- **Cyclic AMP enters cell cytoplasm with message**

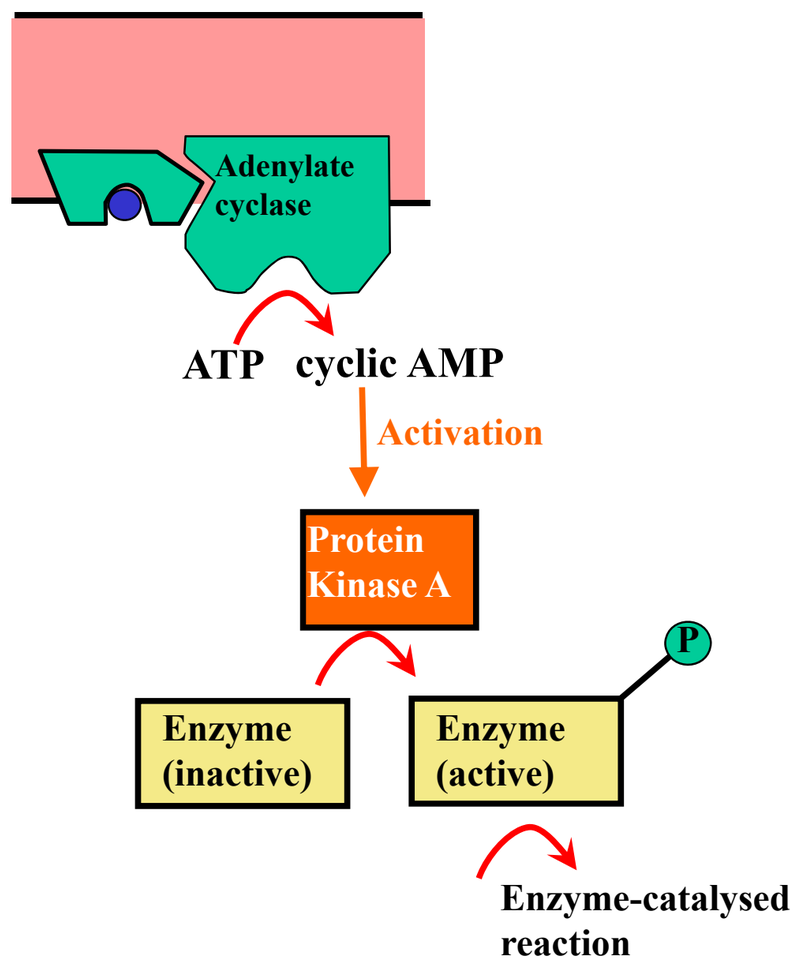


1.3 Interaction of cyclic AMP with protein kinase A (PKA)

- PKA belongs to a group of enzymes called the serine–threonine kinases which catalyse the phosphorylation of serine and threonine residues in protein substrates
- Activated by cyclic AMP
- Phosphate unit provided by ATP

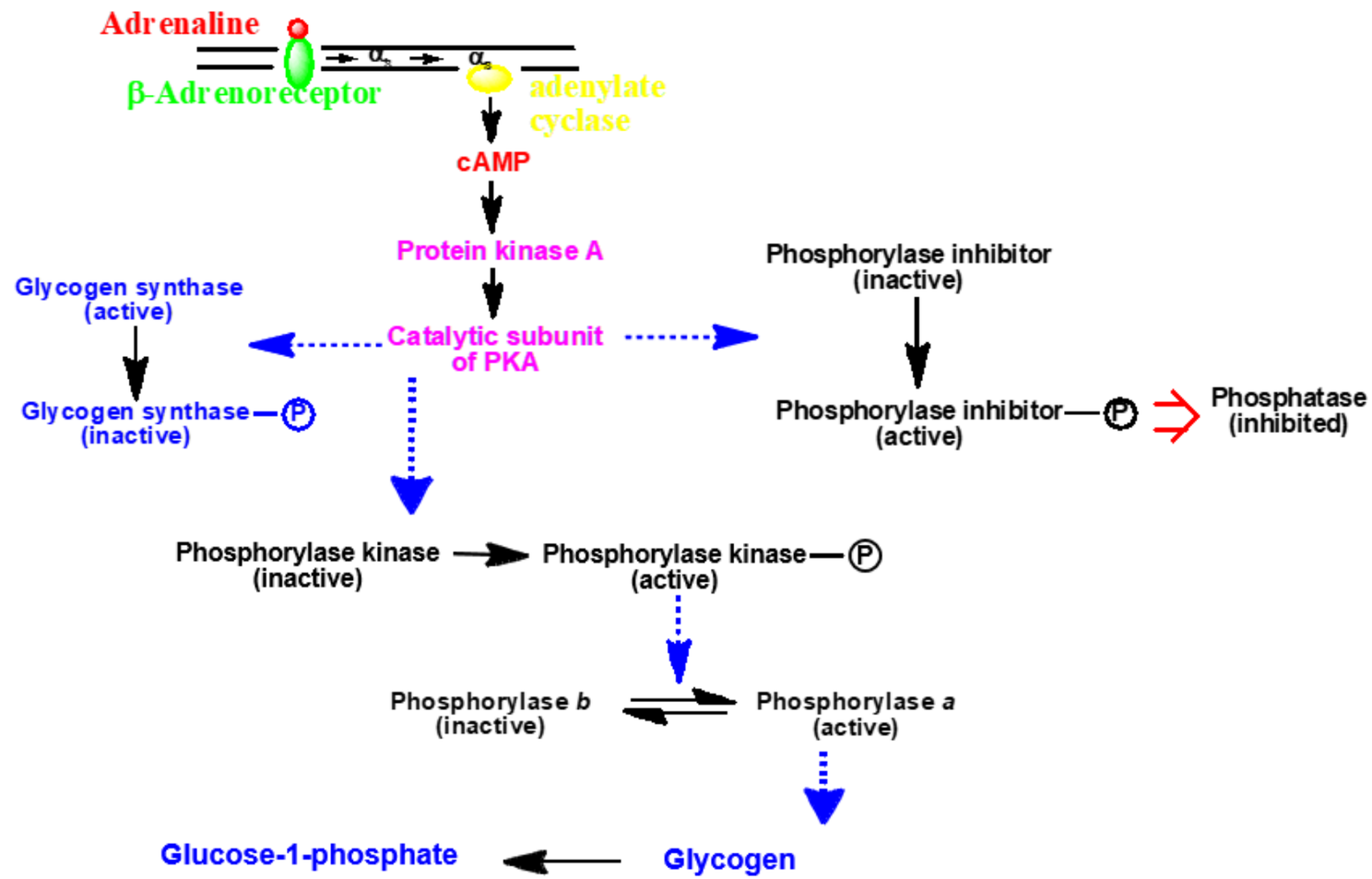


The active site of a protein kinase has to be capable of binding the region of the protein substrate which is to be phosphorylated, ATP which provides the necessary phosphate group



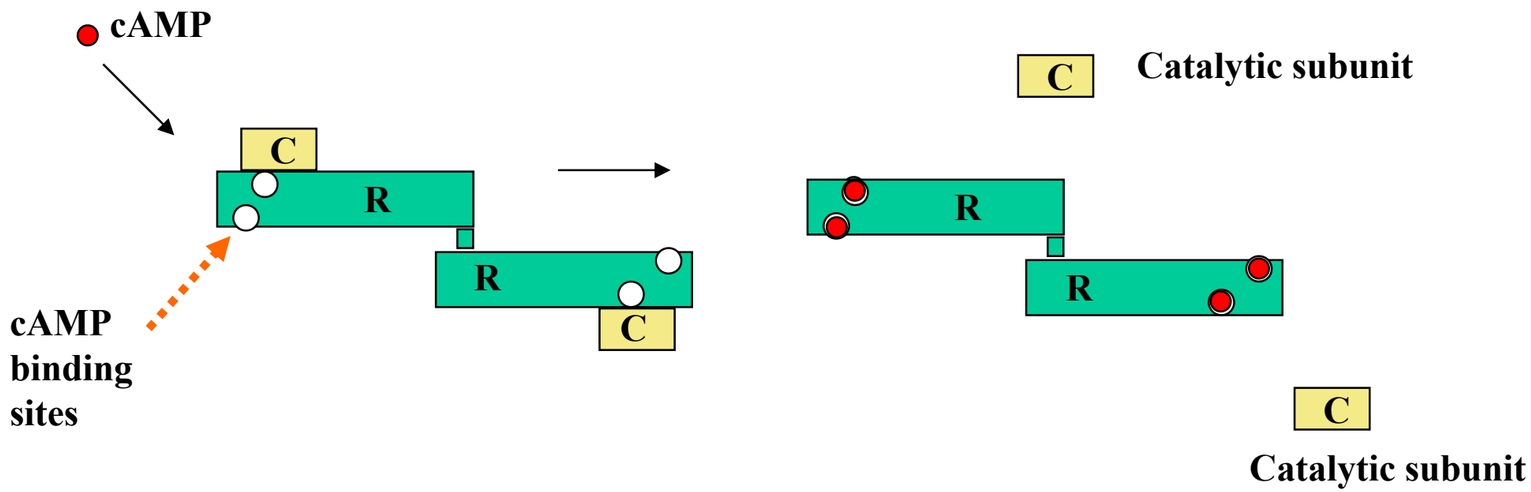
There may be several more enzymes involved in the signalling pathway between the activation of PKA and the activation (or deactivation) of the target enzyme. For example, the enzymes involved in the breakdown and synthesis of glycogen in a liver cell are regulated.

There may be several more enzymes involved in the signalling pathway between the activation of PKA and the activation (or deactivation) of the target enzyme. Case Study: the enzymes involved in the breakdown and synthesis of glycogen in a liver cell (Glycogen metabolism)



For example lipase enzymes in fat cells are activated to catalyse the breakdown of fat.

Protein kinase A **- 4 protein subunits**
- 2 regulatory subunits (R) and 2 catalytic subunits (C)



Note:
- **Cyclic AMP binds to PKA**
- **Induced fit destabilises complex**
- **Catalytic units released and activated**

2. Signal Transduction involving G_i-Proteins

- The enzyme adenylate cyclase is activated by the αs-subunit of the Gs-protein. Adenylate cyclase can also be inhibited by a different G-protein the Gi-protein.

- Receptors that bind Gi-proteins include the muscarinic M2 receptor of cardiac muscle, α2-adrenoceptors in smooth muscle, and opioid receptors in the central nervous system.

- A neurotransmitter which stimulates the production of cAMP forms a receptor–ligand complex which activates a Gs-protein, whereas a neurotransmitter which inhibits the production of cAMP forms a receptor–ligand complex which activates a Gi-protein.

Two different neurotransmitters can have opposing effects at a target cell

Case Study:

noradrenaline interacts with the β-adrenoceptor to activate adenylate cyclase because the β-adrenoceptor binds the Gs-protein. However, noradrenaline interacts with the α2-adrenoceptor to inhibit adenylate cyclase because this receptor binds the Gi-protein.

3. Phosphorylation Reactions

- Phosphorylation is a key reaction in the activation or deactivation of enzymes.
- ATP required as a source for the phosphate group
- Occurs on the phenolic group of tyrosine residues and on the alcohol groups of serine and threonine.
- Phosphorylation introduces two negatively charged oxygens, can form strong ionic bonds with a positively charged group in the protein causing the enzyme to change its tertiary structure. This change in shape results in the exposure or closure of the active site